Amyloid beta peptide cleavage by kallikrein 7 attenuates fibril growth and rescues neurons from Abeta mediated toxicity in vitro.

Journal: Biol Chem

Publication Year: 2013

Authors: Tyler D Shropshire, Jack Reifert, Sridharan Rajagopalan, David Baker, Stuart C Feinstein, Patrick S Daugherty

PubMed link: 23989112

Funding Grants: Training Program in Stem Cell Biology and Engineering

Public Summary:
The gradual accumulation and assembly of beta-amyloid (Abeta) peptide into neuritic plaques is a major pathological hallmark of Alzheimer's disease (AD). Proteolytic degradation of Abeta is an important clearance mechanism under normal circumstances, and it has been found to be compromised in those afflicted with AD. Here, the extended substrate specificity and Abeta-degrading capacity of kallikrein-7 (KLK7), a protease enzyme that degrades other proteins, was characterized. It was found that treatment of Abeta preparations with KLK7 significantly reduced Abeta mediated toxicity to rat hippocampal neurons Taken together, these results indicate that KLK7 possesses an Abeta degrading activity that could be useful in designing drugs to treat Alzheimer's Disease.

Scientific Abstract:
Abstract The gradual accumulation and assembly of beta-amyloid (Abeta) peptide into neuritic plaques is a major pathological hallmark of Alzheimer's disease (AD). Proteolytic degradation of Abeta is an important clearance mechanism under normal circumstances, and it has been found to be compromised in those afflicted with AD. Here, the extended substrate specificity and Abeta-degrading capacity of kallikrein-7 (KLK7), a serine protease with a unique chymotrypsin-like specificity, was characterized. Preferred peptide substrates of KLK7 identified using a bacterial display substrate library were found to exhibit a consensus motif of RXcapital EF, Cyrillic(Y/F) downward arrow(Y/F) downward arrow(S/A/G/T) or RXcapital EF, Cyrillic(Y/F) downward arrow(S/T/A) (capital EF, Cyrillic = hydrophobic), which is remarkably similar to the hydrophobic core motif of Abeta (K16L17V18F19F20A21) that is largely responsible for aggregation propensity. KLK7 was found to cleave after both Phe residues within the core of Abeta42 in vitro thereby inhibiting Abeta fibril formation and promoting degradation of preformed fibrils. Finally, treatment of Abeta oligomer preparations with KLK7, but not inactive pro-KLK7, significantly reduced Abeta42 mediated toxicity to rat hippocampal neurons to the same extent as the known Abeta-degrading enzyme IDE. Taken together, these results indicate that KLK7 possesses an Abeta degrading capacity that can ameliorate the toxic effects of the aggregated peptide in vitro.